REMARKS

Entry of the foregoing, reexamination and reconsideration of the above-identified application are respectfully requested.

Claims 12 and 21 have been amended to change "patient" to "human patient." In view of this amendment, claims 25 and 26 are being canceled. No new matter is added by this amendment. Nor are any new issues raised since dependent claim 25 previously was directed to "human" patients.

In accordance with the request in the Official Action, the non-elected claims (claims 7, 8, 11, 18, 22 and 23) have been canceled. Applicants reserve the right to file a divisional application directed to these claims during the pendency of this application.

Claims 2, 4-6, 9, 10, 12-17, 19-21, 24-26 and 28-30 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Li et al or Takeda et al. This rejection is respectfully traversed.

According to the Official Action, the instant claims encompass the treatment of animals, which would include mice. As amended, the claims are now directed to treatment of human patients. Treatment of mice is no longer encompassed by any of the claims.

The cited art is unrelated to treatment of leukemias in humans. The references disclose studies in mice and make no disclosure regarding the treatment of humans. That the claimed harringtonines would be useful for the treatment of humans, as found by applicants, would not have been expected in light of this prior art.

As noted in the Official Action, applicants' claims are directed to subcutaneous mode of administration for treatment of humans. By contrast, the prior art teaches i.p.

mode of injection for treatment of mice. The use of i.p. mode of injection would not teach or even suggest applicants' method employing a subcutaneous mode of injection. One skilled in the art would not employ an i.p. mode of injection for treatment of humans. One skilled in the art would recognize that an i.p. mode of injection is too dangerous to be used on human patients.

While the i.p. administration route was well known in mice for a long time (Li et al., Takeda et al articles have a date of publication of respectively 1983 and 1982), prior to applicants' invention, the homoharringtonine was previously only administrated by intravenous injection in human beings. It was never disclosed nor suggested that the subcutaneous mode of administration could be used on human beings.

On the contrary, it is well known in the art that for a great number of anti-cancer compounds subcutaneous mode of administration is dangerous. The reason is because of local toxicity, such as tissues necrosis. This is true, for example, for the antracyclin series, i.e., toxorubicin, dororubicin and mitroxartrone, of anti-cancer compounds.

Moreover, the use of homoharringtonine by bolus intravenous injection causes cardiac problems such as hypotension because of the appearance of a homoharringtonine peak in blood. It is for this reason that continuous intravenous administration is preferred on human beings as compared to bolus or rapid intravenous injection. *See, for example,* Stewart et al, *Investigational New Drugs* 3:279-86 (1985), and Malamud et al, *AACR Abstracts*, p. 179, Abstract No. 709 (1984), enclosed herewith. Therefore, at the time of applicants' invention, one skilled in the art would have believed that the subcutaneous route of administration would provoke the appearance of a homoharringtonine peak in blood, and

thus also produce the same toxic effect on the heart as the bolus or rapid intravenous injection. Surprisingly, applicants' invention shows that, although the administration causes the appearance of such a peak, it is not toxic and no cardiac problem or hypotension has been discovered in human beings resulting from the claimed method of treatment.

Furthermore, applicants have shown that for the same dose, the subcutaneous mode of administration is at least as effective as the intravenous mode of administration. This fact was neither described nor suggested in the prior art. One skilled in the art would have expected subcutaneous administration to be much less effective. It should be noted that in more than thirty studies involving homoharringtonine, the subcutaneous mode of administration was never used. *See,* page 6 of the specification.

Applicants' subcutaneous mode of administration, however, has many advantages over the intravenous mode of administration. For example: (i) the patient can self inject the product; (ii) risks of septicaemia by the introduction of germs are null; (iii) overdoses are not possible, and (iv) subcutaneous mode of administration consists in discontinuous injection which permits the synchronization of the cellular cycle which is beneficial for the therapy (all the cells are in the same multiplication phase). This synchronization is impossible, for example, when using continuous intravenous administration. The instant invention thus offers many advantageous and beneficial results, which were not expected prior to applicants' findings. *See also,* page 7, line 30 - page 8, line 30.

Still further, the use of salt forms of harringtonine and homoharringtonine, as claimed herein, is not disclosed or suggested in the prior art. Applicants surprisingly found that "the formulation of salt form of harringtonines administered in mammals by the

subcutaneous mode of administration has had much better bioavailability than the base form of the alkaloids harringtonine used in early clinical trials." Page 7 of the specification. As shown in Example 2, in particular Figures 1 and 2, of the specification, the bioavailability of the salt form of homoharringtonine is considerably higher (triple) that of the base form of this alkaloid in humans. Such an increase of bioavailability of the salt form would not have been expected prior to applicants' invention.

In view of the above, withdrawal of the rejection of record under §103(a) is thus respectfully requested. Such action is believed to be in order.

It is respectfully submitted that all rejections have been overcome by the above amendments. Thus, a Notice of Allowance is respectfully requested.

In the event that there are any questions relating to this amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney at (508) 339-3684.

Respectfully submitted,

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Date: December 18, 2002

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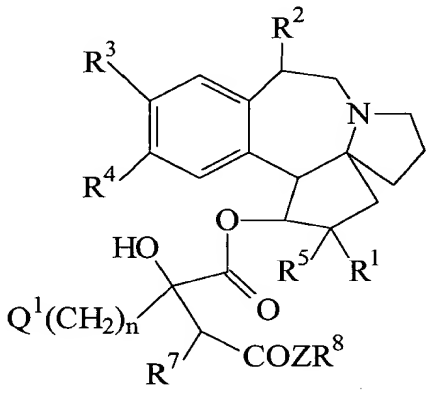
Marked-up Claims 12, 21 and 28

12. (Amended) A method of treating leukemia comprising administering to a human patient in need of such treatment using a subcutaneous mode of administration a harringtonine having the formula



wherein:

- R^1 is H, OH, OMe, O-(C_1-C_{30})-alkyl, O-aryl-(C_1-C_{30})-alkyl, O-(C_2-C_{30})-alkenyl, O-(C_3-C_{30})-cycloalkyl or null and

  R^2 is H or OH, or R^1, R^2 form together -O-,

  R^3 = R^4 = OMe or R^3 and R^4 form together -OCH_2O-,

- n is 0 to 8,

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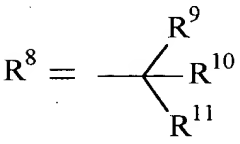
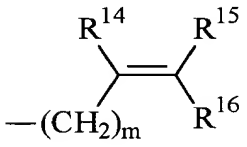
- R^5 is H, OH, OMe, O-(C_1-C_{30})-alkyl, O-aryl-(C_1-C_{30})-alkyl, O-(C_2-C_{30})-alkenyl, O-(C_3-C_{30})-cycloalkyl or O-aryl,

  Z = O, S, or NH, and



  or Z-R^8 is $NR^{12}R^{13}$, R^{12} and R^{13} representing respectively R^9 and R^{10},

  R^9, R^{10}, R^{11} are independently H, C_1-C_{30} alkyl, C_3-C_{30} cycloalkyl, aryl, aryl-(C_1-C_{30})-alkyl, C_2-C_{30} alkenyl, C_2-C_{30} alkynyl, C_1-C_{30} trihalogenoalkyl, C_1-C_{30} alkylamino-(C_1-C_{30})alkyl, C_1-C_{30} dialkylamino(C_1-C_{30})-alkyl, amino-(C_1-C_{30})-alkyl, or



  where R^{14}, R^{15}, R^{16} are independently H, halogen, C_1-C_{30} alkyl, C_3-C_{30} cycloalkyl, aryl, aryl-(C_1-C_{30})-alkyl, C_2-C_{30} alkenyl or C_2-C_{30} alkynyl, or C_1-C_{30} trihalogenoalkyl, and m is 0 to 4,

  each of these groups including or not heteroatom(s),

or salt or tautomeric form thereof.

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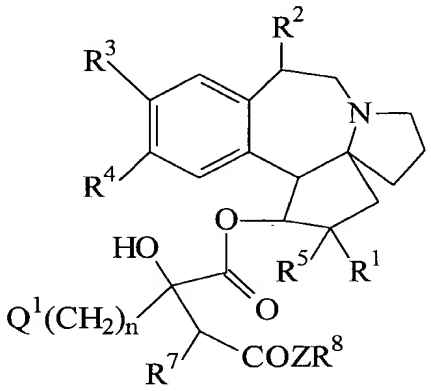
Marked-up Claims 12, 21 and 28

21. (Amended) A method of treating leukemia comprising administering to a human patient in need of such treatment using a subcutaneous mode of administration a harringtonine having the formula



wherein:

- R^1 is H, OH, OMe, O-(C_1-C_{30})-alkyl, O-aryl-(C_1-C_{30})-alkyl, O-(C_2-C_{30})-alkenyl, O-(C_3-C_{30})-cycloalkyl or null and

  R^2 is H or OH, or R^1, R^2 form together -O-,

  R^3 = R^4 = OMe or R^3 and R^4 form together -OCH_2O-,

- n is 0 to 8,

- R^5 is H, OH, OMe, O-(C_1-C_{30})-alkyl, O-aryl-(C_1-C_{30})-alkyl, O-(C_2-C_{30})-alkenyl, O-(C_3-C_{30})-cycloalkyl or O-aryl,

  Z = O, S, or NH, and

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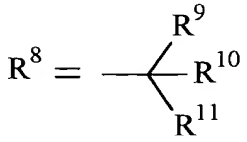
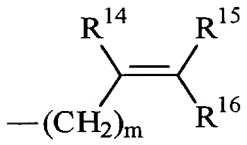
Marked-up Claims 12, 21 and 28



or Z-R^8 is $NR^{12}R^{13}$, R^{12} and R^{13} representing respectively R^9 and R^{10},

R^9, R^{10}, R^{11} are independently H, C_1-C_{30} alkyl, C_3-C_{30} cycloalkyl, aryl, aryl-(C_1-C_{30})-alkyl, C_2-C_{30} alkenyl, C_2-C_{30} alkynyl, C_1-C_{30} trihalogenoalkyl, C_1-C_{30} alkylamino-(C_1-C_{30})alkyl, C_1-C_{30} dialkylamino(C_1-C_{30})-alkyl, amino-(C_1-C_{30})-alkyl,

or



where R^{14}, R^{15}, R^{16} are independently H, halogen, C_1-C_{30} alkyl, C_3-C_{30} cycloalkyl, aryl, aryl-(C_1-C_{30})-alkyl, C_2-C_{30} alkenyl or C_2-C_{30} alkynyl, or C_1-C_{30} trihalogenoalkyl, and m is 0 to 4,

each of these groups optionally including heteroatom(s),

or salt or tautomeric form thereof,

wherein said harringtonine is in a formulation in which

(i) the pH of the formulation is between 5.5 and 8.5,

(ii) the harringtonines are in solution or hydrophilic freeze-dried powder ready-to-reconstitute of buffered salt of homoharringtonine or harringtonine, and

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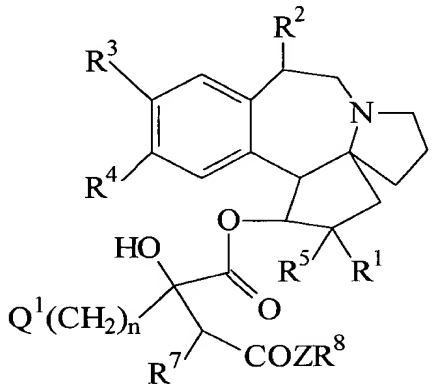
Marked-up Claims 12, 21 and 28

(iii) the level of chromatographic purity of harringtonine is higher than 99.7%.

28. (Amended) A method of treating leukemia comprising administering to a human patient in need of such treatment using a subcutaneous mode of administration a harringtonine salt or tautomeric form thereof, wherein the harringtonine has the formula



wherein:

- R^1 is H, OH,

  OMe, O-(C_1-C_{30})-alkyl, O-aryl-(C_1-C_{30})-alkyl, O-(C_2-C_{30})-alkenyl, O-(C_3-C_{30})-cycloalkyl or null and

  R^2 is H or OH, or R^1, R^2 form together -O-,

  R^3 = R^4 = OMe or R^3 and R^4 form together -OCH_2O-,

- n is 0 to 8,

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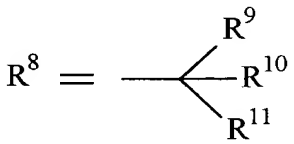
Marked-up Claims 12, 21 and 28

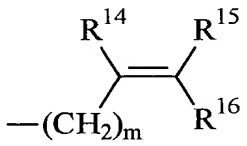
- R^5 is H, OH, OMe, O-(C_1-C_{30})-alkyl, O-aryl-(C_1-C_{30})-alkyl, O-(C_2-C_{30})-alkenyl, O-(C_3-C_{30})-cycloalkyl or O-aryl,

  Z = O, S, or NH, and



or Z-R^8 is $NR^{12}R^{13}$, R^{12} and R^{13} representing respectively R^9 and R^{10},

R^9, R^{10}, R^{11} are independently H, C_1-C_{30} alkyl, C_3-C_{30} clcloalkyl, aryl, aryl-(C_1-C_{30})-alkyl, C_2-C_{30} alkenyl, C_2-C_{30} alkynyl, C_1-C_{30} trihalogenoalkyl, C_1-C_{30} alkylamino-(C_1-C_{30})alkyl, C_1-C_{30} dialkylamino(C_1-C_{30})-alkyl, or amino-(C_1-C_{30})-alkyl, or



where R^{14}, R^{15}, R^{16} are independently H, halogen, C_1-C_{30} alkyl, C_3-C_{30} cycloalkyl, aryl, aryl-(C_1-C_{30})-alkyl, C_2-C_{30} alkenyl or C_2-C_{30} alkynyl, C_1-C_{30} trihalogenoalkyl, m is 0 to 4,

each of these groups optionally including heteroatom(s),

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wherein said harringtonine is in a formulation in which

(i) the pH of the formulation is between 5.5 and 8.5,

(ii) the harringtonines are in solution or hydrophilic freeze-dried powder ready-to-reconstitute of buffered salt of homoharringtonine or harringtonine, and

(iii) the level of chromatographic purity of harringtonine is higher than 99.7%.